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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
ZARA, JANE J

ART UNIT	PAPER NUMBER
1635	22

DATE MAILED: 10/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/243,102	Applicant(s) MACLACHLAN ET AL.	
	Examiner Jane Zara	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *29-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28 and 35-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communications filed July 15, 2002, Paper Nos. 20 and 21.

Claims 1-46 are pending in the instant application, claims 29-34 have been withdrawn from consideration, and claims 1-28, 35-46 have been examined on their merits as indicated below.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 15, 3003 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Maintained Rejections

The declaration filed July 15, 2002, has been entered and considered but does not overcome the rejection for the reasons indicated in the paragraphs which address the enablement rejection directly below.

Claims 1-28, 35-46 are rejected under 35 U.S.C. 112, first paragraph, for lacking enablement for the reasons of record set forth in the Office actions mailed April 10, 2000, January 11, 2002 and October 10, 2001, Paper Nos. 5, 8 and 12 respectively.

Applicant's arguments filed July 15, 2002 have been fully considered but they are not persuasive. Applicants argue that the claims are fully enabled by the instant disclosure because sufficient information has been provided to practice the invention claimed and the experimentation required to practice the invention over the scope claimed would not require undue experimentation. The claims are drawn to methods for treating any neoplasia in a mammal comprising the distal administration of a nucleic acid fully encapsulated within a serum stable nucleic acid lipid particle. Contrary to Applicants' assertions, the ability to treat any neoplastic condition comprising the delivery of a nucleic acid fully encapsulated within a nucleic acid lipid particle is a highly unpredictable endeavor. Successful therapeutic effects cannot be predicted for any and/or all forms of neoplasia in any mammal without undue experimentation beyond that provided in the instant disclosure. In vivo efficacy utilizing gene therapy depends on a myriad of factors, including the type of neoplasia being treated and the type of nucleic acid being delivered within the nucleic acid lipid particle. Applicants have provided numerous examples of successful in vitro cell and in vivo tumor delivery, as well as tumor reduction using particular lipid nucleic acid compositions for the lipid nucleic acid particles which contain encapsulated nucleic acids. The success obtained with the particular lipid nucleic acid compositions, however, is not representative of the ability to successfully treat any and/or all

neoplasias in a mammal by administering any nucleic acid encapsulated within any lipid nucleic acid particle.

Applicants' declaration and the arguments filed July 15, 2002 delineate various experiments which provide treatment effects for various neoplasias in animal models, including: delivery of a reporter genes to Lewis lung carcinoma cells and human colon adenocarcinoma cells in mice; tumor (B16 mouse melanoma cells) growth reduction in mice following administration (which mode of administration was not delineated) of polynucleotide encoding HSV-TK encapsulated in lipid nucleic acid particles; tumor (fibrosarcoma cells and colorectal cancer cells) growth reduction in mice following intravenous administration of HSV-TK encapsulated within lipid nucleic acid particles combined with intraperitoneal administration of ganciclovir; tumor (MCA-207 sarcoma cells) growth reduction in mice following administration (mode undisclosed) of a polynucleotide encoding IL-12 encapsulated in lipid nucleic acid particles; tumor (CT26 colon carcinoma cells) growth reduction in mice following administration (mode undisclosed) of a polynucleotide encoding either apoptin or pseudomonas exotoxin. The disclosure also teaches the reduction of tumor cell growth in vitro following transfection of various target cells lines with polynucleotides encoding purine nucleoside phosphorylase combined with 2-fluoroadenine, or transfected with a polynucleotide encoding cytosine deaminase, which polynucleotides were encapsulated within a lipid nucleic acid particle.

These experiments illustrate the ability to treat various tumor models in mice using recombinant HSV-TK, IL-12, apoptin, pseudomonas exotoxin, encapsulated in lipid nucleic acid

particles with defined lipid compositions. These modes of treatment are not representative of the ability to treat any neoplasia in any mammal comprising the administration of any nucleic acid encapsulated in any lipid nucleic acid particle, but are representative of the ability to treat the various neoplasias described, using the polynucleotides described and comprising the mode of administration utilized and the particular lipid nucleic acid compositions utilized for such treatments.

Investigators throughout the world are currently attempting to generate and/or optimize treatment methods for a multitude of cancers using gene therapy approaches, including targeted delivery of appropriate recombinant polynucleotides for a particular neoplastic condition, as well as utilizing antisense and ribozymes to target appropriate target genes which are involved in various neoplastic conditions. In addition, many investigators have been optimizing gene delivery approaches using various delivery devices, including liposomes, virally or bacterially derived delivery vehicles, and lipid nucleic acid particles that encapsulate nucleic acids or other labile drugs (e.g. see the references of Hung et al and Kirn cited below), and success depends on the delivery device used, the target organ or target cell involved, the recombinant nucleic acid or drug used and the type of neoplasia treated, all of which must be determined empirically. Therefore, it would require undue experimentation beyond that which has been taught in the instant disclosure to enable one to treat any neoplasia in any mammal comprising the administration of any nucleic acid encapsulated in any lipid nucleic acid particle.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 4, line 2, it is unclear what the term "gene is exogenous" means. (Exogenous to what?). Appropriate correction is requested.

In claim 6, line 5, it is unclear what the term "analogs thereof" is referring to. Appropriate correction is requested.

In claim 7, line 2, it is unclear what the term "gene is homologous" is referring to. Appropriate correction is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim is drawn to a method of treating a neoplasia in a mammal comprising the administration of a gene encoding a member selected from the group consisting of HSV-TK, cytosine deaminase, xanthine-guaninephosphoribosyl transferase, purine nucleoside phosphorylase, cytochrome P450 2B1, and analogs therof.

The specification and claims do not indicate what distinguishing attributes are concisely shared by the members of the genus comprising analogs of HSV-TK, cytosine deaminase, xanthine-guaninephosphoribosyl transferase, purine nucleoside phosphorylase and cytochrome P450 2B1. No common structural attributes identify the members of this genus. The scope of the claim includes numerous structural variants, and genus is highly variant because a significant number of structural differences between genus members is permitted. Since the disclosure fails to describe the common attributes or characteristics concisely identifying members of the proposed genus from others, and because the genus is highly variant, the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus comprising analogs of HSV-TK, cytosine deaminase, xanthine-guaninephosphoribosyl transferase, purine nucleoside phosphorylase and cytochrome P450 2B1. Thus, Applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).
(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-4, 8, 10-12, 16-18, 23, 28, 42, 44, 46 are rejected under 35 U.S.C. 102(e) as being anticipated by Kirn et al.

Kirn et al teach methods of treating neoplasia in a mammal comprising the administration (at a site distal to the neoplasia) of a serum stable, nucleic acid lipid particle comprising a fully encapsulated nucleic acid encoding a therapeutic, proto-oncogenic polynucleotide, and which lipid portion of the particle comprises a cationic lipid, and optionally further comprises a neutral lipid, which lipids include DOTMA, DOPE, cholesterol and DC-Chol, and which nucleic acid to

lipid ratio is greater than about 3 mg nucleic acid per mmole of lipid, which administration is performed at least once per eight weeks (See entire document, especially col. 2, lines 21-64; col. 7, lines 15-36; col. 8, line 53-col. 9, line 63; col. 10, line 20- col. 12, line 34; examples 2 and 3, col. 12-14).

Claims 1-4, 8, 10-12, 16-18, 23, 28, 39-42, 44, 46 are rejected under 35 U.S.C. 102(e) as being anticipated by Hung et al.

Hung et al teach methods of treating neoplasia in a mammal comprising the administration (at a site distal to the neoplasia) of a serum stable, nucleic acid lipid particle comprising a fully encapsulated nucleic acid encoding a therapeutic, proto-oncogenic polynucleotide, and optionally further comprising administration of a chemotherapeutic agent either before or after administration of the nucleic acid lipid particle, and which lipid portion of the particle comprises a cationic lipid and optionally further comprises a neutral lipid, and which lipids include DOTMA, DOPE, cholesterol and DC-Chol, which nucleic acid to lipid ratio is greater than about 3 mg nucleic acid per mmole of lipid, and which administration is performed at least once per eight weeks (See entire document, especially col. 8, lines 3-34; col. 9, lines 27-54; col. 11, line 25-col. 12, line 14; col. 18, lines 26-67; col. 24, line 23-col. 26, line 56; col. 28-32; examples II-VI, col. 38-48).

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A Lacourciere

KAREN LACOURCIERE
PATENT EXAMINER

JZ

October 1, 2002